REMARKS

Claims 1, 4, 5, 8-23 and 26-32 were pending prior to this Response. By the present communication, no claims have been added, claims 26 and 27 were canceled without prejudice, and claims 1 and 32 have been amended to define Applicants' invention with greater particularity. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Specifically, support for the amended claims may be found, among others, in the specification at page 2, lines 3-18; at page 3, lines 9-10; at page 12, lines 3-15; and at page 16, lines 11-12, of the specification as filed. Accordingly, claims 1, 4, 5, 8-23 and 28-32 are currently pending in this application.

Rejection of under 35 U.S.C. §102

Applicants respectfully traverse the rejection of claims 1, 4, 5, 8-17, 19-23, and 29-32 under 35 U.S.C. §102(a) as allegedly being anticipated by Parnot, et al. (hereinafter, "Parnot"). To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). M.P.E.P. § 2131.

The Office action alleges that Parnot teaches a method of constructing a library of mutated angiotensin II type 1A receptors by *randomly* mutating the receptor to generate *every possible mutation*, on average five substitutions per residue, and expressing the library in mammalian cells (emphasis added). Applicants respectfully submit that the assays of Parnot relate to the regular function of the selected protein. In other words, Parnot discloses methods of finding every possible way to constitutively activate a receptor of known function (*i.e.*, angiotensin II type 1A).

Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claims 1 and 32 to require identification of small or medium side-chain amino acid residues of a candidate orphan receptor that are located in or proximate to a transmembrane segment of the orphan receptor. As such,

Applicants submit that the claimed invention requires identification of a limited number of possible mutations for an orphan receptor (*i.e.*, a receptor of unknown function) that "are most likely to contribute to conformational changes in the mutant receptor that result in activation." (Specification, page 11, lines 18-19). No prior knowledge of the receptor's activity is required. The library provided by the claimed invention is generated by replacing only coding sequences for the identified small or medium side-chain amino acids with coding sequences for large side-chain amino acids. "The larger side-chains will then force the protein to adopt a different conformation, or prevent interaction with another molecule." (Specification, page 12, lines 9-11). Thus, the mutagenic approach of the claimed invention gives "rise to forms of the receptor in which the steady-state equilibrium of the receptor is shifted towards the active form (R*) relative to the wild-type receptor." (Specification, page 11, lines 21-23).

Since Parnot fails to disclose *identifying* small or medium side-chain amino acid residues of a candidate *orphan* receptor that are located in or proximate to a transmembrane segment of the orphan receptor, Applicants respectfully submit that Parnot fails to disclose each and every element of the claimed invention, and request withdrawal of the rejection.

Rejection of under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Parnot in view of King et al. (hereinafter "King"). The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385), modified the standard for establishing a prima facie case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Office Action alleges that Parnot teach a reporter construct which expresses a luminescent protein. Applicants submit that the arguments presented above with regard to Parnot apply equally are incorporated herein. The Office relies upon King as allegedly teaching constructing a heterologous reporter system by combining the *E.coli*-β-galactosidase gene (lacZ) under yeast pheromone responsive FUS1 promoter to study G protein coupled receptor activation. However, Applicants submit that King is absolutely silent with regard to identifying small or medium side-chain amino acid residues of a candidate orphan receptor that are located in or proximate to a transmembrane segment of the orphan receptor. Accordingly, one of the skill in the art would not have been motivated to combine Parnot and King to arrive at the claimed invention.

Even if one of skill in the art were motivated to combine Parnot and King, Applicants submit that doing so would not yield the claimed method for identifying constitutively activating mutations in an orphan receptor or an ion channel since neither reference discloses use of a receptor of unknown function *and* identification of the small or medium side-chain amino acid residues that are located in or proximate to a transmembrane segment of the orphan receptor. Accordingly, since the combined references do not teach each and every limitation of the amended claims, Applicants respectfully submit that *prima facie* obviousness of the invention over Parnot and King, either alone or in combination, has not been shown by the Examiner, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 27 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Parnot in view of Moore, et al. (hereinafter "Moore"). Applicants have canceled claim 27 without prejudice, rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claim 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Parnot in view of Lerner, et al. (hereinafter "Lerner"). Applicants submit that the arguments presented above with regard to Parnot apply equally are incorporated herein. The Office relies upon Lerner as allegedly disclosing a method of

identifying antagonists or agonists for G-protein coupled receptors using a pigment cell. However, Lerner is absolutely silent with regard to identifying small or medium side-chain amino acid residues of a candidate orphan receptor that are located in or proximate to a transmembrane segment of the orphan receptor. Accordingly, one of the skill in the art would not have been motivated to combine Parnot and Lerner to arrive at the claimed invention.

Even if one of skill in the art were motivated to combine Parnot and Lerner, Applicants submit that doing so would not yield the claimed method for identifying constitutively activating mutations in an orphan receptor or an ion channel since neither reference discloses use of a receptor of unknown function *and* identification of the small or medium side-chain amino acid residues that are located in or proximate to a transmembrane segment of the orphan receptor. Accordingly, since the combined references do not teach each and every limitation of the amended claims, Applicants respectfully submit that *prima facie* obviousness of the invention over Parnot and Lerner, either alone or in combination, has not been shown by the Examiner, and request withdrawal of the rejection.

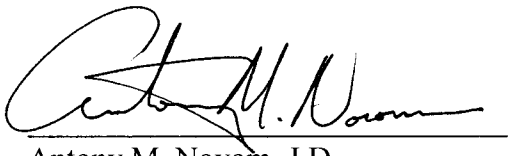
Applicants respectfully submit that *prima facie* obviousness of the invention over the cited references, either alone or in combination, has not been shown by the Examiner. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103 for alleged lack of patentability are respectfully requested.

Conclusion

In summary, for the reasons set forth herein, Applicants submit that the amended clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $60.00 as payment for the Petition for One-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-referenced Attorney docket number.

Respectfully submitted,



Date: November 12, 2007

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